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# Chronic fatigue syndrome (CFS/ME) symptom-based phenotypes and 1-year treatment outcomes in two clinical cohorts of adult patients in the UK and The Netherlands

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## ABSTRACT

**Objective:** We previously described symptom-based chronic fatigue syndrome (CFS/ME) phenotypes in clinical assessment data from 7041 UK and 1392 Dutch adult CFS/ME patients. Here we aim to replicate these phenotypes in a more recent UK patient cohort, and investigate whether phenotypes are associated with 1-year treatment outcome.

**Methods:** 12 specialist CFS/ME services (11 UK, 1 NL) recorded the presence/absence of 5 symptoms (muscle pain, joint pain, headache, sore throat, and painful lymph nodes) which can occur in addition to the 3 symptoms (post-exertional malaise, cognitive dysfunction, and disturbed/unrefreshing sleep) that are present for almost all patients. Latent Class Analysis (LCA) was used to assign symptom profiles (phenotypes). Multinomial logistic regression models were fitted to quantify associations between phenotypes and overall change in health 1 year after the start of treatment.

**Results:** Baseline data were available for  $N = 918$  UK and  $N = 1392$  Dutch patients, of whom 416 (45.3%) and 912 (65.5%) had 1-year follow-up data, respectively. 3- and 4-class phenotypes identified in the previous UK patient cohort were replicated in the new UK cohort. UK patients who presented with 'polysymptomatic' and 'pain-only' phenotypes were 57% and 67% less likely (multinomial odds ratio (MOR) 0.43 (95% CI 0.19–0.94) and 0.33 (95% CI 0.13–0.84)) to report that their health was "very much better" or "much better" than patients who presented with an 'oligosymptomatic' phenotype. For Dutch patients, polysymptomatic and pain-only phenotypes were associated with 72% and 55% lower odds of improvement (MOR 0.28 (95% CI 0.11, 0.69) and 0.45 (95% CI 0.21, 0.99)) compared with oligosymptomatic patients.

**Conclusions:** Adult CFS/ME patients with multiple symptoms or pain symptoms who present for specialist treatment are much less likely to report favourable treatment outcomes than patients who present with few symptoms.

## 1. Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or, more recently in the USA, systemic exertion intolerance disease (SEID) [1], is defined as persistent or recurrent debilitating fatigue that is not lifelong, or the result of ongoing exertion, or alleviated by rest, or explained by other conditions, and that results in a substantial reduction in activity [2,3]. A meta-analysis of studies based on clinically-confirmed cases in several countries indicated a prevalence of 0.76% (95% CI 0.23% to 1.29%) [4]. CFS/ME imposes a huge burden on patients, careers and families [5,6]. In the UK, adults who attend NHS specialist CFS/ME services have been ill for a median

duration of 3 years, and half of those employed at the onset of their illness have ceased working [7].

In a previous study, we used latent class analysis to identify CFS/ME 'phenotypes' based on symptoms in CFS/ME patients attending UK specialist CFS/ME services from 2010 to 2013 [8]. Post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms. The other 5 symptoms (muscle pain, joint pain, headache, sore throat, and painful lymph nodes) delineated 3 phenotypes, characterized as 'polysymptomatic', 'oligosymptomatic', and 'pain-only' [8]. We replicated these 3 phenotypes in a cohort of CFS/ME patients attending a Dutch specialist CFS/ME service and, in both cohorts, the phenotypes were strongly associated with patient-

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reported measures of illness severity and with comorbidities.

The two aims of the present study were: 1) to replicate the original symptom-based CFS/ME phenotypes in a new UK cohort of CFS/ME patients; and 2) to investigate whether phenotypes were related to patient-reported treatment outcomes in the new UK cohort and in the original Dutch patient cohort.

## 2. Methods

### 2.1. UK CFS/ME patient cohort

Patients were recruited from 11 specialist CFS/ME services across England (10 NHS services, 1 registered independent provider) during the period 01/06/2014 to 30/09/2016. Patients were eligible if they were  $\geq 18$  years old and had a CFS/ME diagnosis made or confirmed at an initial clinical assessment appointment in accordance with NICE guidelines [2]. Patients were assessed and treated by clinicians and therapists who have specialist training and experience in the diagnosis and treatment of CFS/ME. The assessment included recording the presence/absence of 12 pre-specified symptoms, under guidance that the symptom should have persisted/recurred during  $\geq 4$  consecutive months, did not predate the fatigue and was not caused by some other medical condition. The 12 symptoms were: sleep disturbance/unrefreshing sleep; joint pain; muscle pain; headaches; painful lymph nodes; sore throat; cognitive dysfunction; post-exertional malaise; general malaise/flu-like symptoms; dizziness; nausea; palpitations. Clinicians also recorded the presence/absence of common comorbidities, including migraine, Irritable Bowel Syndrome (IBS), Fibromyalgia, depression, and anxiety. At the time of their initial assessment, patients completed standard questionnaires to obtain quantitative measures of fatigue (Chalder Fatigue Scale [9] and Checklist Individual Strength (CIS20-R) [10]) and physical function (RAND SF-36 [11]). Approximately 12 months after their initial clinical assessment, patients were asked to rate changes in their overall health on a Clinical Global Impression scale. They were asked “Overall, how much do you feel your health has changed since you first came to the CFS/ME service?” with possible responses of “very much”, “much” or “a little” better, “no change”, or “very much”, “much” or “a little” worse. Patients who didn't respond were contacted by the clinical team via phone or email on up to 2 further occasions to elicit a response. Outcomes were coded as ‘Much better’ (= “Very much better” or “Much better”), ‘Worse’ (= “Very much worse” or “Much worse”) or ‘Unchanged’ (= “A little better”, “No change” or “A little worse”).

### 2.2. Dutch CFS/ME patient cohort

The Dutch cohort comprised adults diagnosed with CFS/ME and treated at a tertiary specialist care centre during the period 2007–2012 in accordance with Centers for Disease Control and Prevention (CDC) criteria [3,12] and Dutch guidelines [13,14]. A Checklist Individual Strength (CIS20-R) fatigue subscale score  $\geq 35$  [10] and a Sickness Impact Profile (SIP) score  $\geq 700$  were used as operational criteria for fatigue that was severe enough to cause substantial functional impairment [15]. Consultants in the outpatient clinic of the Department of Internal Medicine assessed the medical status of all patients, and decided whether patients had been sufficiently evaluated to rule out an alternative explanation for their fatigue. Patients were given a full physical examination (unless this had already been completed), case history evaluation and laboratory tests. CDC diagnostic criteria include a set of 8 persistent/recurrent symptoms occurring during 6 or more consecutive months: unrefreshing sleep; pain in several joints; muscle pain; headache; tender lymph nodes; sore throat; impaired memory; impaired concentration; and feeling ill after exertion. Patients were asked “Which of the following complaints did you experience during the last 6 months?” and, if affirmative, whether the symptom had been experienced for “less than” or “longer than” 6 months. We coded

responses of “Not at all” and “Sometimes (each month)” as ‘symptom absent’ and responses of “Sometimes (each week)” and “Daily” as ‘symptom present’. The latter also required the symptom to have been experienced for “longer than” 6 months. ‘Post-exertional malaise’ was in response to a question asking whether symptoms were worse after physical effort; ‘Cognitive dysfunction’ was based on an affirmative response to one or both of two separate questions about forgetfulness and concentration; ‘Sleep disturbance’ was in response to a question asking whether the patient woke up unrefreshed. Responses were recorded by self-completed questionnaire. Patients completed the CIS20-R after 12 months' follow up. Patients were classified as ‘Much better’ if their 12-month follow-up CIS20-R fatigue and SF-36 physical function subscale scores were ‘normal’ ( $< 35$  and  $\geq 65$ , respectively) [15] and if their fatigue had decreased by  $\geq 8$  points (corresponding to  $1.96 \times \text{Reliable Change Index (RCI)}$ , where  $\text{RCI} = \sqrt{2} \times \text{SD}_{\text{healthy population}} \times \sqrt{(1 - \text{Cronbach } \alpha)}$  [16]. For the CIS20-R fatigue subscale,  $\alpha = 0.93$  and  $\text{SD}_{\text{healthy population}} = 10.75$  [17]. Patients' health was classified as ‘Worse’ if their fatigue score had increased, and all other patients were classified as ‘Unchanged’.

### 2.3. Ethical approvals

The UK study had NHS Research Ethics Committee approval (14/NW/0242), and all patients provided written informed consent. The medical-ethical committee of the Radboud University Nijmegen Medical Centre ruled that the collection and analysis of Dutch CFS/ME patient data did not require ethical review. Dutch CFS/ME patient data were collected as part of routine clinical practice.

### 2.4. Statistical methods

#### 2.4.1. CFS/ME phenotypes

CFS/ME phenotypes in the UK patient cohort were explored using the same method as described in our earlier study [8]. Post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms, therefore we based our analysis on the five other symptoms recorded in both cohorts, namely: muscle pain, joint pain, headache, sore throat, and painful lymph nodes (dizziness, nausea, and palpitations were recorded only in the UK cohort). We used latent class analysis (LCA) to identify subtypes of related cases (latent classes, or ‘phenotypes’) according to presence/absence of each symptom [18]. Patients are ‘assigned’ (probabilistically) to one of a pre-defined number of discrete latent classes based on the presence or absence of symptoms. The optimum class solution, i.e. the optimum number of classes, is selected by inspection and comparison of various model fit statistics [19], including: 1) Bayesian Information Criterion (BIC); 2) bivariate model fit - a test of the conditional independence assumption (within each class, there should be no association of one symptom with another, because all associations between symptoms are accounted for by class membership); 3) entropy - a measure of how well individuals have been classified (based on class membership probabilities) - a value of ‘1’ indicates perfect separation of the classes; 4) Lo-Mendell-Rubin adjusted likelihood ratio test for  $c$  compared with  $c-1$  classes; and 5) bootstrapped likelihood ratio test (BLRT) for  $c$  compared with  $c-1$  classes. Selection of the optimum latent class solution, particularly when the statistical selection criteria are inconclusive, may also be informed by subjective input, including: clinical/biological plausibility, prior knowledge of likely heterogeneity within CFS/ME, and the clinical and epidemiological utility of any solution. The probabilities of reporting each symptom across the latent classes obtained from the original and new UK patient datasets were compared by visual inspection.

#### 2.4.2. Associations of CFS/ME phenotypes with patient-reported outcome

Multinomial odds ratios (MORs) adjusted for age and sex were estimated using multinomial logistic regression with a 3-level ordinal

outcome variable ('Much better', 'Unchanged' (reference), or 'Worse'). We used an implementation in Mplus version 7.11 (Muthén and Muthén, 2013) of the 3-step method proposed by Jeroen Vermunt [20,21]. Models were derived initially using the normative latent class as the baseline category for the outcome. The models were then reparameterized to investigate possible differences between the classes, using each class in turn as reference class. This method has been shown to produce less biased estimates than traditional 3-step methods, such as probability weighting and modal class assignment, whilst avoiding the problem of covariates impacting on the measurement model itself [20]. To investigate whether our symptom-based phenotypes were associated with outcomes at 1 year independently of severity of illness, we further adjusted our MORs for baseline fatigue and physical function. Mean values of baseline fatigue and physical function across the latent classes and associations of sex, age group and comorbidities with latent classes were estimated using the same 3-step approach.

### 3. Results

#### 3.1. UK and Dutch patient characteristics

Baseline data were available for 918 UK and 1392 Dutch patients. Demographic characteristics of UK and Dutch patients were broadly similar (Table 1), although the Dutch cohort was slightly younger (median 37 (IQR 27–46)) years compared to 41 (30–50) years ( $p = 0 < 0.001$ ) and had a slightly higher proportion of men (25.6% (356/1036) compared to 19.0% (174/918),  $p < 0.001$ ). Dutch patients had higher SF36 physical function scores (median 55 (40–70) compared to 40 (25–60),  $p < 0.001$ , high score = less disabled). 12-month follow-up data were available for 416 (45.3%) UK and 912 (65.5%) NL patients. UK patients lost to follow-up were slightly younger than those who had follow-up data (mean 39.6 vs 42.1 years,  $p = 0.005$ ) but there were no differences in sex or baseline fatigue and physical function. Dutch patients lost to follow-up were slightly older than those who had follow-up data (mean 38.2 vs 36.7 years,  $p = 0.02$ ), were more likely to be male (28.8% vs 23.9%) and had

**Table 1**  
Characteristics of UK and Dutch adult CFS/ME patient cohorts.

	UK patients (N = 918)	Dutch patients (N = 1392)	P-value <sup>a</sup>
	Median (IQR) or n (%)	Median (IQR) or n (%)	
Age (years)	41 (30–50)	37 (27–46)	$p < 0.001$
Sex (female)	744 (81.1%)	1036 (74.4%)	$p < 0.001$
Symptoms			
Muscle pain	766 (83.4%)	948 (68.1%)	$p < 0.001$
Joint pain	644 (70.2%)	808 (58.1%)	$p < 0.001$
Headaches	605 (65.9%)	760 (54.6%)	$p < 0.001$
Painful lymph nodes	402 (43.8%)	309 (22.2%)	$p < 0.001$
Sore throat	497 (54.1%)	251 (18.0%)	$p < 0.001$
CIS20-R fatigue score (range 8–56)	50 (46–53)	51 (47–55)	$p < 0.001$
SF-36 physical function (range 0–100)	40 (25–60)	55 (40–70)	$p < 0.001$
Follow-up at 1 year	416 (45.3%)	912 (65.5%)	$p < 0.001$
Overall improvement at 1 year <sup>b</sup>			
Unchanged	264 (63.5%)	301 (33.0%)	$p < 0.001$
Much better	115 (27.6%)	545 (59.8%)	
Worse	37 (8.9%)	66 (7.2%)	

<sup>a</sup> Kruskal-Wallis test for medians, Chi-squared test for proportions.

<sup>b</sup> In UK patients, Clinical Global Impression scale, where 'Much better' = "Very much better" or "Much better", 'Worse' = "Very much worse" or "Much worse" or 'Unchanged' = "A little better", "No change" or "A little worse"; in Dutch patients, change in CIS20-R fatigue score, where 'Much better' = score  $< 35$  and change  $> 7$  and SF-36 score  $\geq 65$ , 'Worse' = change  $< 0$ , 'Unchanged' = all other responses.

worse baseline physical function (mean 54.0 vs 58.4,  $p < 0.001$ ) but there was no difference in baseline fatigue. Overall changes in health were broadly similar in the two cohorts: 27.6% of UK patients reported their health to be very much or much better, 63.5% reported little or no change, and 8.9% said that their health was worse, compared with 59.8%, 33.0%, and 7.2% of Dutch patients classified (by fatigue and physical function score) as much better, unchanged or worse, respectively ( $p < 0.001$ ).

#### 3.2. CFS/ME phenotypes in UK patient cohort

The 3- and 4-class solutions previously identified in Dutch and UK patient cohorts were replicated in the new UK patient cohort (Figs. 1 & 2, Table S1). As before, classes in the 3-class solution represented 'polysymptomatic', 'pain only', and 'oligosymptomatic' phenotypes, and the 4-class solution delineated an additional 'sore throat/painful lymph node/headache' phenotype. The proportions of patients assigned to each of the classes in the 3-class solution were similar in the new vs original UK patient cohorts: 'polysymptomatic' 53.4% vs 53.2%; 'pain-only' 32.7% vs 37.6%; and 'oligosymptomatic' 13.9% vs 9.2% (Fig. 1). There were greater differences in the distribution of patients across the 4-class solution in the new vs original UK patient cohorts: 17.9% vs 8.2% 'oligosymptomatic'; 16.4% vs 10.2% 'sore throat/painful lymph node/headache'; and 25.7% vs 36.6% 'pain-only' (Fig. 2). No associations between sex and phenotype were evident (Table S2). Dutch patients 40–59 years old were much more likely to a pain or polysymptomatic phenotype, compared with patients age 18–29 years (Table S2). No associations between age and phenotype were evident for UK patients. In both cohorts, baseline fatigue and physical function were indicative of more severe illness in pain and polysymptomatic cf. oligosymptomatic patients (Table S2).

Patients presenting with a polysymptomatic phenotype were more likely to have comorbid migraine, IBS, depression, and anxiety compared to oligosymptomatic patients (Table S2). Fibromyalgia as a comorbidity was reported for 36% and 24% of patients classified with pain and polysymptomatic phenotypes, respectively; too few oligosymptomatic patients (3%) had comorbid fibromyalgia to allow estimation of odds ratios using this phenotype as the reference group.

#### 3.3. Associations of CFS/ME phenotypes with treatment outcomes

Using the 3-class solution, UK and Dutch patients presenting with polysymptomatic and pain only phenotypes were much less likely to report substantial improvement in their health at 12 months, compared to patients presenting with the oligosymptomatic phenotype (Table 2). Adjusted multinomial odds ratios (MOR) showed that, compared with oligosymptomatic patients, UK patients who were polysymptomatic were 58% less likely to report their health as being 'much better' (MOR = 0.42 (95% CI 0.20, 0.89)) and patients with predominantly pain-only symptoms were 65% less likely (MOR = 0.35 (0.15, 0.82)) to report substantial improvement. Similar effects were seen in polysymptomatic and pain-only Dutch patients, who were respectively 51% (MOR = 0.49 (0.31, 0.80)) and 42% (MOR = 0.58 (0.39, 0.88)) less likely to be classified as being much better. There were no associations between phenotypes and substantially worse health, although estimates were imprecise because of the relatively small numbers of patients whose health had deteriorated. Further adjustment of the MORs for baseline fatigue and physical function changed the UK estimates slightly, the Dutch estimates to a greater degree (towards bigger effects), but the overall pattern of effects was unchanged and evidence remained for inverse associations of polysymptomatic and pain only phenotypes with much improved health (Table 2).

### 4. Discussion

Symptom-based CFS/ME phenotypes that we identified in a

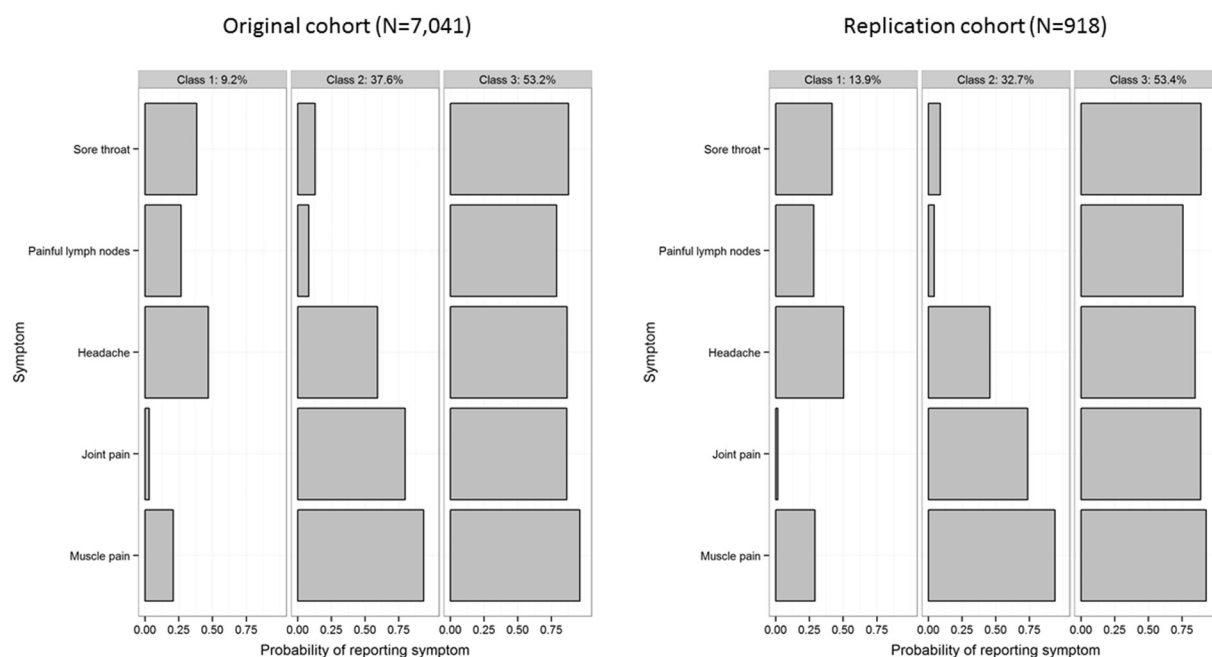


Fig. 1. 3-class solution based on 5 symptoms in UK adult CFS/ME patient cohorts.

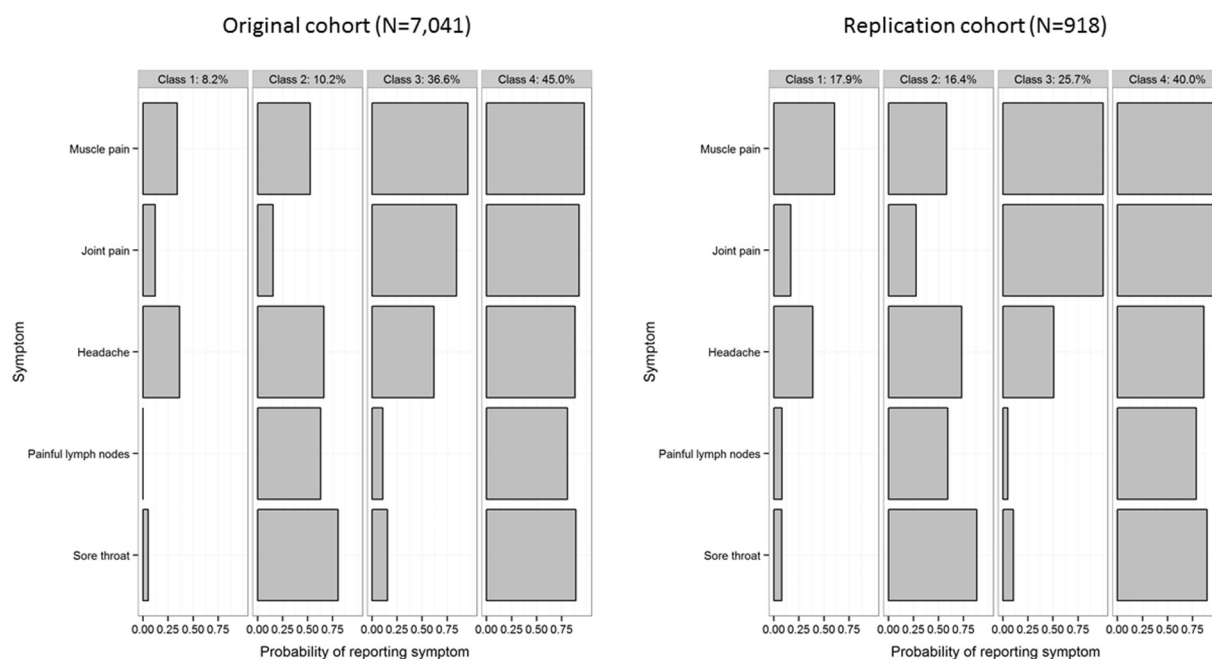


Fig. 2. 4-class solution based on 5 symptoms in UK adult CFS/ME patient cohorts.

previous UK clinical cohort of adult CFS/ME patients were replicated in a new UK cohort of patients. These phenotypes were associated with treatment outcomes, in that patients who presented with multiple symptoms (in addition to post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep) or with pain as additional symptoms were much less likely to experience a substantial improvement in their health one year after the start of treatment. These associations were similar in UK and Dutch patients, and were robust to adjustment for severity of illness at initial clinical assessment (most notably, a higher level of physical function in Dutch patients).

The main strengths of our study lie in the large sample sizes of our patient cohorts, and that all patients were diagnosed at specialist CFS/ME services in either secondary (UK) or tertiary (NL) specialist CFS/ME facilities. The main limitations of our study are that improvement in

health one year after treatment was measured differently in UK and Dutch patients, and the UK cohort had high losses to follow up. For UK patients, we relied on patients' self-reported impression of their overall improvement in health, and for Dutch patients we calculated a reliable change index. The aim of our study was to investigate whether phenotypes were associated with patient-reported treatment outcomes, rather than to quantify precisely any such associations. This means that the magnitude of the observed effects should be interpreted cautiously, and our results should instead be interpreted in terms of the consistency of effects across the two cohorts - namely, that patients with 'poly-symptomatic' and 'pain-only' phenotypes were much less likely to benefit from specialist treatment in either the UK or the Netherlands. This consistency was observed despite between-cohort differences in diagnostic criteria and patient characteristics. Treatment outcome in

**Table 2**

Overall change in health in UK and Dutch adult CFS/ME patients according to symptom-based phenotype (latent class).

	UK adult CFS/ME patients			Dutch adult CFS/ME patients		
	Class 1 (15.5%)	Class 2 (35.5%)	Class 3 (49.0%)	Class 1 (22.6%)	Class 2 (51.9%)	Class 3 (25.4%)
	Oligosymptomatic	Pain only	Polysymptomatic	Oligosymptomatic	Pain only	Polysymptomatic
		Multinomial odds ratio (95% CI) <sup>a</sup>	Multinomial odds ratio (95% CI) <sup>a</sup>	(Reference)	Multinomial odds ratio (95% CI) <sup>a</sup>	Multinomial odds ratio (95% CI) <sup>a</sup>
Much better (cf. unchanged)	Reference	0.35 (0.15, 0.82)	0.42 (0.20, 0.89)	Reference	0.58 (0.39, 0.88)	0.49 (0.31, 0.80)
Worse (cf. unchanged)	Reference	1.47 (0.32, 6.75)	0.52 (0.10, 2.66)	Reference	0.85 (0.38, 1.92)	1.07 (0.44, 2.58)
		Further adjusted multinomial odds ratio (95% CI) <sup>b</sup>	Further adjusted multinomial odds ratio (95% CI) <sup>b</sup>		Further adjusted multinomial odds ratio (95% CI) <sup>b</sup>	Further adjusted multinomial odds ratio (95% CI) <sup>b</sup>
Much better (cf. unchanged)	Reference	0.33 (0.13, 0.84)	0.43 (0.19, 0.94)		0.45 (0.21, 0.99)	0.28 (0.11, 0.69)
Worse (cf. unchanged)	Reference	1.33 (0.27, 6.46)	0.50 (0.10, 2.48)		0.83 (0.52, 1.31)	0.88 (0.52, 1.49)

<sup>a</sup> Adjusted for age and sex.<sup>b</sup> Adjusted for age, sex and baseline fatigue and physical function (UK patients - Chalder Fatigue Scale, SF-36 physical function subscale; Dutch patients - CIS20-R fatigue subscale, SF-36 physical function subscale).

the UK cohort may have been biased by differential losses to follow up, but phenotype was not associated with loss to follow up, and we have no reason to suspect that the association between phenotype and outcome was biased. The generalizability of our findings is limited in that the two cohorts comprised people who had access to specialist services, representing an unknown proportion of all potential patients. Our original study in UK patients found a 6-class solution based on nine symptoms (the five in the present study, plus dizziness, nausea, and palpitations) [8]. The 3-class solution in the present study arose because we wanted to compare associations of phenotypes with treatment outcomes between the UK and Dutch cohorts. The small number of symptoms common to both cohorts, and the smaller size of these cohorts relative to the original UK cohort, precluded replication of the 6-class solution. The simpler 3-class solution shares key features with the 6-class solution, namely the poorer baseline health status and more likely occurrence of comorbidities among polysymptomatic patients.

Our outcomes were defined to differentiate patients who had improved, rather than attempting to define 'recovery', which is a complex (and controversial) topic in CFS/ME [22–24]. Treatment effects at the Dutch specialist service in our study were better than a comparable UK specialist service (not involved in our study), a difference which persisted after adjusting for baseline characteristics [25]. The higher proportion of Dutch vs UK patients who were classified as 'much better' in our study (59.8% vs 27.6%) may be a true difference in treatment outcomes (we did not have data to compare the intensity and duration of treatments received), or a consequence of the different definitions of improvement, or because Dutch patients had levels of physical function commensurate with less severe illness at baseline, or a combination of all three.

Although many patients derive substantial benefit from treatments provided by specialist services, there remain in both countries groups of patients who do not improve, and a small group whose condition is worse at follow up [26,27]. Our findings show that patients with different phenotypes have different prognoses. From a CFS/ME specialist service perspective, this might suggest the importance of individualised treatment, for example, for patients with pain symptoms, who have less favourable treatment outcomes [28–30]. However, from a broader healthcare perspective, it could be argued that a more comprehensive framework of clinical management of patients with symptom-based diagnoses/functional somatic symptoms is needed [31,32]. From this perspective, the setting of our study within the boundaries of specialist

CFS/ME services (well established in the UK and the Netherlands, much less so in most other countries) could be perceived as a limitation. Whether multiple symptoms and functional somatic symptoms delineate subtypes of CFS/ME [33–35], whether CFS/ME is a subtype of an umbrella syndrome [36], or whether distinct syndromes such as CFS/ME and fibromyalgia simply occur comorbidly [37] remains an open question. The answer has major implications for clinical research and practice, including the design of clinical trials [38] and the role of illness severity rather than symptomatology in predicting treatment outcomes [39].

## 5. Conclusion

The total number of symptoms and the presence of pain symptoms (in addition to the cardinal symptoms of CFS/ME, namely post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep) are important predictors of treatment outcome in adult CFS/ME patients.

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## Competing interests

All authors have completed the Unified Competing Interest form at [www.icmje.org](http://www.icmje.org). EC is a medical advisor for the Sussex & Kent ME/CFS Society.

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